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Effect of mechanical ventilation guided by transpulmonary pressure in acute respiratory distress syndrome patients: a systematic review and meta-analysis of randomized control trials

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Abstract. – OBJECTIVE: This study aimed to investigate the effect of mechanical ventilation guided by transpulmonary pressure in patients diagnosed with acute respiratory distress syndrome (ARDS).

MATERIALS AND METHODS: Randomized control trials of ARDS patients that received mechanical ventilation guided by transpulmonary pressure *vs.* mechanical ventilation guided by traditional lung protective ventilation strategies in adults were retrieved by two reviewers independently from PubMed, EMBASE, The Cochrane Library, The China National Knowledge Infrastructure, and WanFang database before October 2022. The protocol has been registered on PROSPERO (CRD42022307816). The primary outcome was mortality. The secondary outcomes included mechanical ventilation days, oxygenation function and ventilation parameters, hemodynamics, and cytokines level.

RESULTS: Thirteen articles (819 patients) were finally included through our search strategy. The total mortality (RR, 0.68; 95% CI, 0.54-0.85; *p* = 0.0006) and mechanical ventilation days (MD, -2.77; 95% CI, -4.60 – -0.94; *p* = 0.003) reduced when compared with the control group. Patients in the transpulmonary pressure group had higher oxygen index (MD, 40.74; 95% CI 9.81-71.68, *p* = 0.010) and lung compliance (MD, 7.98; 95% CI 4.55-11.41, *p* < 0.00001). Positive end-expiratory pressure (PEEP) was higher in the transpulmonary pressure group (MD, 5.47; 95% CI, 3.59 - 7.35; *p* < 0.00001). The Interlukin-6 (IL-6) level in the control group decreased obviously compared with that in the transpulmonary pressure group (SMD, -2.03; 95% CI, -3.50 – -0.56; *p* = 0.007).

CONCLUSIONS: Mechanical ventilation guided by transpulmonary pressure tended to have a beneficial prognosis on ARDS patients. Oxygenation and lung mechanics parameters were also improved. The clinical effect of mechanical ventilation directed by transpulmonary pressure was superior to the traditional lung protective ventilation strategies in ARDS patients.

Key Words:
Acute Respiratory Distress Syndrome, Mechanical ventilation, Transpulmonary pressure, Positive end-expiratory pressure, Ventilation-induced lung injury, Meta-analysis.

Abbreviations

MD, Mean Difference; SMD, Standardized Mean Difference; CI, Confidence Interval; RR, Risk Ratio; ARDS, Acute Respiratory Distress Syndrome; PEEP, Positive End Expiratory Pressure; TPP, Transpulmonary Pressure; ALI, Acute Lung Injury; MV, Mechanical Ventilation; VILI, Ventilation-induced Lung Injury; RCT, Randomized Control Trail; PROSPERO, Prospective Register of Systematic Reviews; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyzes.

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Introduction

Acute respiratory distress syndrome (ARDS) is a very common clinical problem worldwide[1], and it affects 10% of the patients admitted to critical care units and the mortality is up to 46.1% in severe ARDS patients[1,2]. With the epidemic of severe acute respiratory syndrome coronavirus-2, severe COVID-19 cases evoke acute respiratory distress syndrome[3]. It is well-known that ARDS is a complex and heterogeneous syndrome that is characterized by refractory hypoxemia and respiratory distress with acute diffuse lung injury (ALI)[4,5]. Mechanical ventilation shows its advantages in improving respiratory function and correcting hypoxemia effectively and it is considered the main life-support strategy[6]. The current ventilation strategies in ARDS mainly include lung protective ventilation, optimal PEEP, low driving pressure, recruitment maneuvers, neuromuscular blockade, and prone position[7]. Though multiple ventilation strategies have been proposed, an important complication of mechanical ventilation is ventilation-induced lung injury (VILI), which greatly influences the prognosis of patients with ARDS[8,9]. VILI is caused by the pressure applied to the alveoli, not the airway pressure. A hallmark physiologic concept supporting the risk for VILI is lung stress or transpulmonary pressure[10], although several lines of evidence have documented that lower tidal volumes are beneficial in patients diagnosed with ARDS[11,12]. A low tidal volume of 6 ml/kg is not a safe option for all patients. An essential principle of low Tidal volume lung protection is to reduce lung strain, and non-physiological strain may lead to VILI[13].

Transpulmonary pressure (TPP) distinguishes lung from chest wall mechanics effectively and reflects the true force of overcoming lung elastic resistance to promote alveolar opening[14]. PEEP set by maintaining end-expiratory transpulmonary pressure positive can decrease atelectasis and cyclical opening and closing of airway and alveoli, thus improving lung mechanics[15]. Meanwhile, the end-inspiratory transpulmonary pressure can be used to limit the maximum PEEP value, monitor lung overdistension, and individualize the targeting of tidal volume[16,17]. In 2008, Talmor[18] found that a personalized strategy for tuning PEEP based on patient transpulmonary pressure may be superior to the empirical PEEP tuning according to the ARDS net protocol. Grasso et al[19] conducted an experiment on 36 patients with severe H1N1 infection and found that maintaining the inspiratory transpulmonary pressure of 25 cmH_2O improved oxygenation. While Garegnani et al[20] meta-analyses, which included all critically ill patients requiring mechanical ventilation, suggested no benefit from transpulmonary pressure. Garegnani et al[20] did not classify critical illness and included a small number of studies. However, as the main treatment for ARDS, an appropriate PEEP is important. The usage of transpulmonary pressure could better decrease the complications of inappropriate PEEP, so it seems more meaningful to study whether or not set PEEP by transpulmonary pressure has a better prognosis in ARDS patients. Therefore, the aim of our meta-analysis is to explore whether mechanical ventilation guided by transpulmonary pressure improves prognosis in ARDS patients.

Materials and Methods

This systemic review and meta-analysis were reported following the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy (PRISMA)[21]. The protocol of this review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022307816).

Search Strategy and Study Selection

Randomized controlled trials that compared mechanical ventilation guided by transpulmonary pressure *vs.* mechanical ventilation guided by traditional methods in adults were included in our study. The PICOS criteria were as follows: (1) participants: patients with ARDS and received mechanical ventilation; (2) intervention: transpulmonary pressure monitoring during mechanical ventilation; (3) comparison intervention: mechanical ventilation guided by traditional strategies such as lower tidal volumes, Empirical High PEEP-FiO2 Strategy, best oxygenation or ARDSnet protocol and so on; (4) outcome: mortality was the primary outcome and the secondary outcomes were described as below; (5) study design: randomized control trials.

Studies that complied with the following conditions were admitted to our meta-analysis: adults (age > 18 years) diagnosed with ARDS according to the Berlin definition[5]; accepting mechanical ventilation and monitoring by transpulmonary pressure *vs*. traditional methods; randomized control trials. The non-RCT study, animal experiment, case report, or systematic review were excluded.

Relevant articles were retrieved from PubMed, EMBASE, The Cochrane Library, The China National Knowledge Infrastructure, and WanFang database by using the Mesh Term. There were no language limitations in our study. The last update was on October 20th, 2022. All studies were independently screened by two reviewers (Zhang Q and Li Y), and any disagreements were resolved by a third reviewer (Liu N). More details of our search strategies can be found in the **Supplementary File**.

Data Extraction

Details of population, first author, publication year, study design, number of patients in two groups, transpulmonary pressure limitations, and interventions of the control group were extracted by two independent authors (Zhang Q and Li Y). Any disagreements were resolved by the third reviewer (Liu N).

Outcomes

The primary outcome was the mortality which included total mortality and moderate to severe ARDS mortality (according to the Berlin definition[5] – oxygen index between 100 and 200 was regarded as moderate, and lower than 100 was considered as severe ARDS). The secondary outcomes included the length of mechanical ventilation, oxygenation index, ventilation parameters (PEEP, the plat pressure, the peak airway pressure, lung compliance, respiratory rate, tidal volume, pulmonary volume, and extravascular lung water index), hemodynamics (cardiac index, heart rate, mean arterial pressure, central venous pressure, diastolic blood pressure, and systolic blood pressure) and cytokines levels (Interleukin-6 and Interleukin-8).

Quality Assessment

The risk of bias was assessed by two trained investigators according to Cochrane risk-of-bias instrument. Each item was judged and provided an overall judgment of low risk, high risk, or unclear risk of bias.

Statistical Analysis

Review Manager 5.3 (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark) and Stata 15.0 (StataCorp LP, Stata Statistical Software, TX, USA) were used for data analysis to assess the effect of treatment. Mean deviation (MD) or standardized mean difference (SMD) and 95% confidence interval (CI) were calculated in continuous variables. For dichotomous variables, we calculated the risk ratio (RR) with 95% CI. According to the Cochrane Handbook for Systematic Reviews of Interventions[22], *p*-value < 0.10 indicated that there was a potentially considerable heterogeneity. The heterogeneity of effect sizes was performed with Cochran's Q statistic and the I^2 statistic. A fixed-effect model was employed if p for heterogeneity ≥ 0.1 and $I^2 \leq 50\%$. A random model was considered if *p* for heterogeneity < 0.1 or I^2 > 50%.

Publication bias was tested by the funnel plot and Egger's test. A leave-one-out sensitivity analysis was performed to evaluate the robustness of the assessment[23].

Results

Literature Search

A total of eight hundred and two related studies were admitted to our search strategy from the database published up to October 20th, 2022. Two hundred and forty-nine records were excluded because of duplicates. Five hundred and two records were excluded after reading the abstract. Thirty-eight records were excluded after a further full-text screening due to non-compliance with inclusion criteria and repeated experiments in the same research center during the same period. Eventually, thirteen articles enrolling 819 participants diagnosed with ARDS who underwent mechanical ventilation were admitted to our study (Figure 1). More detailed characteristics of studies are shown in Table I and **Supplementary Table I**.

Risk of Bias and Quality Assessment

All of the included studies[14,18,24-34] mentioned randomization, and twelve studies[14,18,24-31,33-34] described specific randomization methods. The procedures for hidden assignment and blinding were not clear in these twelve studies[18,24-34] . Quality assessment is shown in **Supplementary Figure 1**.

Primary Outcome

Ten articles[14,18,24-27,29,30-32] reported the total mortality. A fixed-effect model was performed for the reason of no heterogeneity (*p* for hetero-

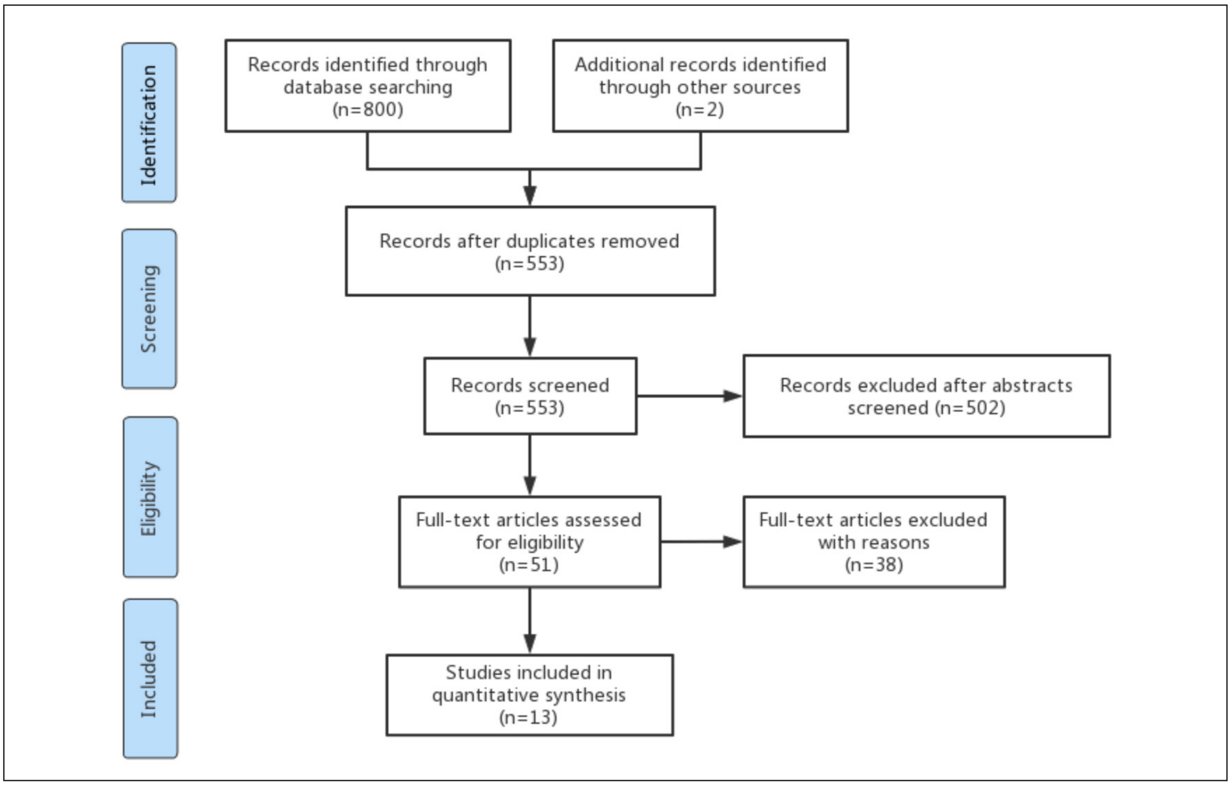

Figure 1. Flowchart of the article selection process according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA).

geneity = 0.28, I^2 = 18%). The sensitivity analysis result showed that the stability was high. There was no publication bias according to Egger's test result (**Supplementary Figure 2**). A significant reduction could be found in the total mortality of mechanical ventilation guided by the transpulmonary pressure group (RR, 0.68; 95% CI, 0.54 - 0.85; p = 0.0006) (Figure 2).

Eight articles[14,18,24,25,29-32] reported moderate to severe ARDS mortality. The use of transpul-

Table I. Characteristics of each study.

References	Year	Study design	Nation	Sample size	Intervention group size	Primary outcome
Huang et al[25]	2022	RCT	China	103	52	Mortality
Lin et al[26]	2020	RCT	China	44	22	Mortality
Wang et al[24]	2020	RCT	China	102	52	Mortality
Jiang et al[27]	2020	RCT	China	40	20	Mortality
Beitler et al[14]	2019	RCT	The United States and Canada	200	102	Mortality
Huang et al[31]	2019	RCT	China	70	35	Mortality
Liu et al[28]	2019	RCT	China	65	33	Tidal volume and lung compliance
Wang et al[33]	2019	RCT	China	23	12	Oxygen index
Wang et al[30]	2018	RCT	China	36	19	Mortality
Jash et al[32]	2018	RCT	N	40	20	Mortality
Li et al[29]	2017	RCT	China	35	14	Mortality
Sarge et al[34]	2014	RCT	The United States	61	30	Mean arterial pressure
Talmor et al[18]	2008	RCT	The United States	61	30	Mortality

RCT: Randomized Clinical Trial.

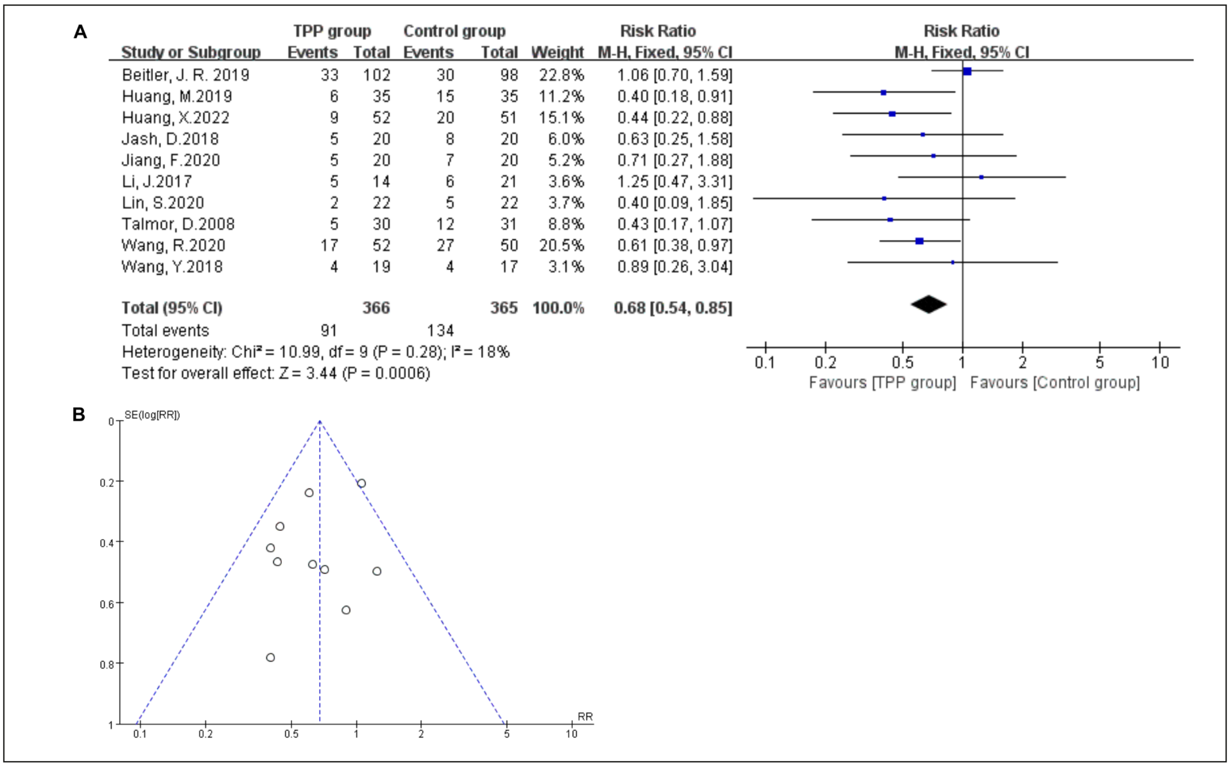

Figure 2. Forest and funnel plots of total mortality in ARDS patients. **A**, Forest plot showing meta-analysis of RR of total mortality in patients with ARDS. **B**, Funnel plot for ARDS total mortality studies.

monary pressure in participants diagnosed with moderate to severe ARDS showed a noted reduction in mortality (RR, 0.69; 95% CI, 0.54-0.86; p = 0.001). No heterogeneity was found in our study (I^2 = 33%; p for heterogeneity = 0.16) (**Supplementary Figure 3**). There was no significant statistical change in when sequential removal of each trial. Egger's test did not show any publication bias (**Supplementary Figure 4**).

Secondary Outcomes

Effect of transpulmonary pressure in patients with ARDS: mechanical ventilation days

Eight studies[14,25-27,30-33] reported the mechanical ventilation days. The random-effect model was conducted after testing the heterogeneity (p for heterogeneity < 0.00001, I^2 = 94%). The Egger's test was used to evaluate the publication bias (**Supplementary Figure 5**). Sensitivity analysis showed the stability of the results by sequentially removing each trial. The mechanical ventilation days in the transpulmonary pressure group were lower according to our result (MD, -2.77; 95% CI -4.60 – -0.94, p = 0.003) (**Supplementary Figure 6**).

Effect of transpulmonary pressure in patients with ARDS: hemodynamics

Meta-analysis for hemodynamics included cardiac index, heart rate, mean arterial pressure, central venous pressure, diastolic blood pressure, and systolic blood pressure. Four studies[26,27,29,30] enrolling 155 participants reported cardiac index. The fixed-effect model was used after testing the heterogeneity (p for heterogeneity = 0.65, I^2 = 0%). Sensitivity analysis and the Egger's test were used to assess the stability of the results and publication bias (**Supplementary Figure 7**). There was a declination in the transpulmonary pressure group when compared with the control group (MD, -3.85; 95% CI -7.08 – -0.62, p = 0.02) (Figure 3).

Four studies[24,26,30,33] reported on the heart rate, three studies[24,26,33] on diastolic blood pressure and systolic blood pressure, six stud-

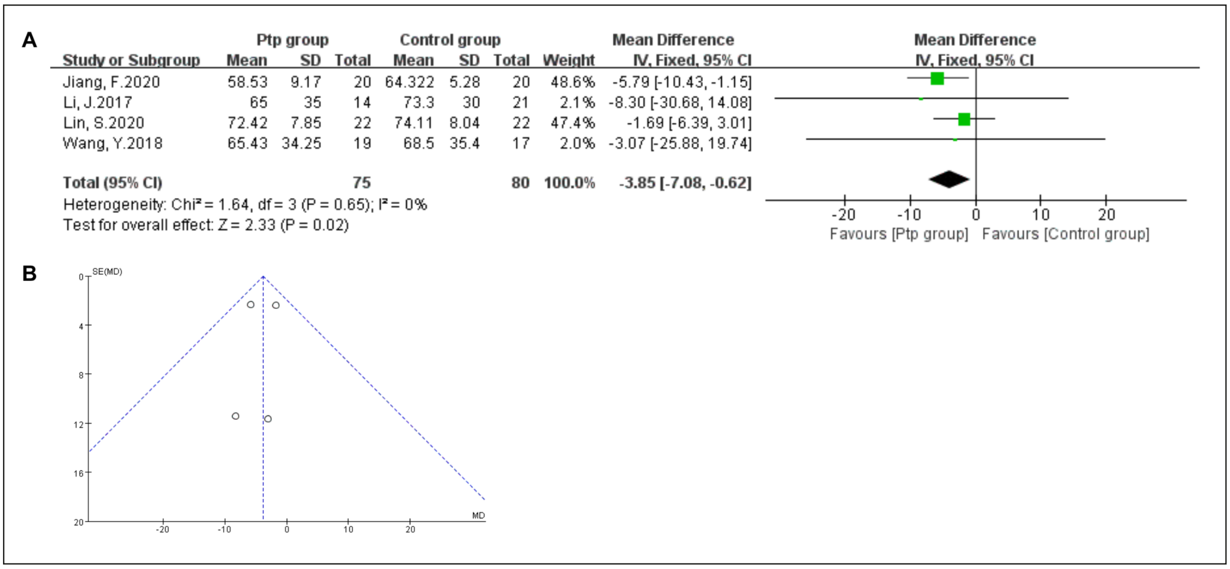

Figure 3. Forest and funnel plots of cardiac index in ARDS patients. **A**, Forest plot showing meta-analysis of MD of cardiac index in patients with ARDS. **B**, Funnel plot for ARDS cardiac index studies.

ies[24,26,27,29,30,34] on mean arterial pressure, and three studies[26,30,33] on central venous pressure. Meta-analyses did not demonstrate differences between the transpulmonary pressure group and the control group (**Supplementary Table II**).

Effect of transpulmonary pressure in patients with ARDS: oxygenation and lung mechanics

Nine studies[18,25,26,28,29-33] met our inclusion criteria, with a total of 477 participants mentioning the oxygen index. The random effect model was used after testing the heterogeneity (p for heterogeneity < 0.00001, I^2 = 98%). Egger's test showed no publication bias (**Supplementary Figure 8**). The sensitivity analysis results showed that the stability was high. The oxygen index in the transpulmonary pressure group was better than the control group (MD, 40.74; 95% CI 9.81 - 71.68, p = 0.010) (Figure 4).

Nine studies[18,24-27,29-31,33] presented results for positive end-expiratory pressure. A random-effects model was conducted after testing the heterogeneity (p for heterogeneity < 0.00001, I^2 = 92%). Publication bias was found through the Egger's test (**Supplementary Figure 9**). Sensitivity analysis showed high stability of the result. MD across the studies was 5.47 (p < 0.00001, 95% CI 3.59 - 7.35) (Figure 5), indicating higher PEEP in the transpulmonary pressure group when compared with the control group.

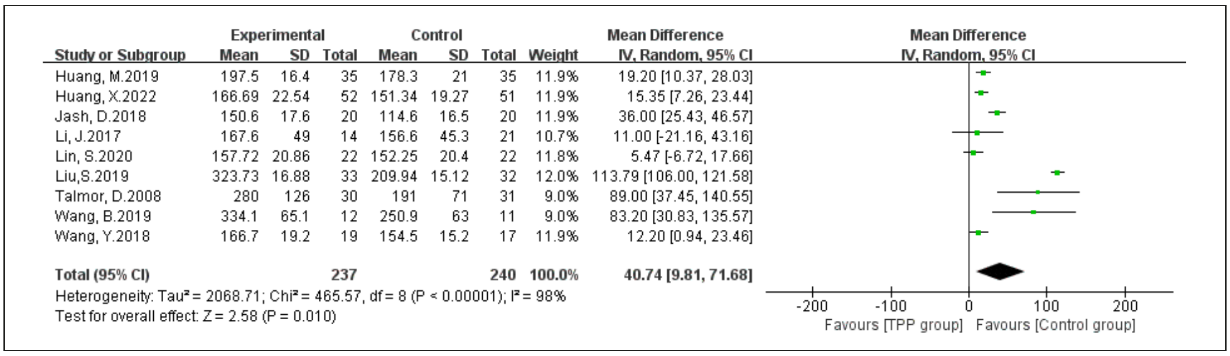

Figure 4. Forest plot showing meta-analysis of MD of oxygen index in patients with ARDS.

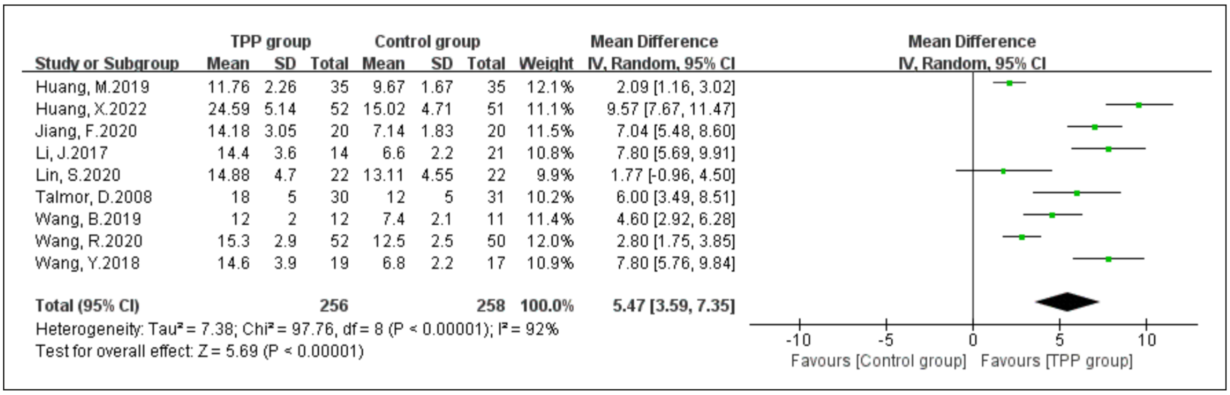

Figure 5. Forest plot showing meta-analysis of MD of positive end expiratory pressure in patients with ARDS.

Five studies[18,24,27,30,33] enrolling 262 patients reported peak airway pressure. Fixed-effect models were used after testing the heterogeneity (p for heterogeneity = 0.34, I^2 = 12%). The sensitivity analysis result showed that the stability was high. Publication bias was found through Egger's test (**Supplementary Figure 10**). The peak airway pressure in the transpulmonary pressure group was higher when compared with the control group (MD, 1.27; 95% CI 0.53-2.01, p = 0.0008) (**Supplementary Figure 11**).

Three studies[18,29,30] enrolling 132 patients reported plateau pressure. A fixed-effect model was conducted after testing the heterogeneity (p for heterogeneity = 0.70, I^2 = 0%). Sensitivity analysis and Egger's test were used to assess the stability of the results and publication bias (**Supplementary Figure 12**). The result showed a higher plateau pressure in the transpulmonary pressure group (MD, 3.99; 95% CI 1.69 - 6.29, p = 0.0007) (**Supplementary Figure 13**).

Eight studies[25-26,28,29-33] presented lung compliance. After the heterogeneity test (p for heterogeneity < 0.00001, I^2 = 87%), a random effect model was conducted. The Egger's test was used to evaluate the publication bias (**Supplementary Figure 14**). Sensitivity analysis showed that the stability was high by sequentially removing each trial. Lung compliance improved in the transpulmonary pressure group when compared with the control group (MD, 7.98; 95% CI 4.55-11.41, p < 0.00001) (**Supplementary Figure 15**).

The results, included the extravascular lung water index[26,29], tidal volume[18,24,28], and respiratory rate[18,24] were presented in **Supplementary Table II**, indicating no evident difference between the transpulmonary pressure group and control group.

Effect of transpulmonary pressure in patients with ARDS: cytokines levels

Two studies[24,33] enrolling 125 patients reported Interleukin-6 and Interleukin-8. Meta-analysis showed that Interleukin-6 was decreased significantly in the transpulmonary pressure group when compared with the control group (SMD -2.03; 95% CI -3.5 – -0.56, p = 0.007, p for heterogeneity = 0.005, I^2 = 87%) (**Supplementary Figure 16**). However, there was no difference in interleukin-8 between the experiment group and the control group (SMD, -0.2; 95% CI -3.35 - 2.94, p = 0.9, p for heterogeneity < 0.00001, I^2 = 97%). We considered the difference of detection mainly took account for the high heterogeneity.

Discussion

The pathogenesis of ARDS involves inflammation-mediated disruptions in alveolar-capillary permeability, severe alveolar edema, extensive alveolar collapse, and decreased lung compliance, resulting in refractory hypoxemia[35,36]. Mechanical ventilation is the mainstay of life-support therapy for ARDS[37]. With an increasing awareness of lung protection which can be accomplished by an applicable PEEP, people are attaching much importance to the "best PEEP" strategy. However, a low-level PEEP setting cannot fully open the collapsed alveoli. Consequently, using a high-level PEEP can lead to ventilation-induced lung injury (VILI), as well as right heart failure and unstable hemodynamics[37-40]. In a randomized controlled trial conducted by Wang et al[24] in 2020, it was found that mechanical ventilation guided by TPP had a beneficial effect on severe ARDS patients, which improved the proportion of weaned from venovenous extracorporeal membrane oxygenation and downregulated the level of inflammation mediators. The results of our meta-analysis show that PEEP directed by TPP has lower mortality, higher lung compliance, and better oxygenation. Additionally, patients in the TPP group had shorter mechanical ventilation days and lower IL-6 levels compared to the control group. There were also statistically significant differences in lung mechanics parameters.

Initially, mortality was significantly reduced in the transpulmonary pressure group by a subgroup analysis, particularly in moderate to severe ARDS patients. A similar result was found by Sarge et al[41], who re-analyzed the EPVent-2 trial and found that MV guided by transpulmonary pressure could decrease mortality in comparison with the control group in moderate to severe ARDS. Meanwhile, mortality declined sharply when PEEP was titrated to end-expiratory transpulmonary pressure near 0 cm H_2O, promoting the reopening of collapsed alveoli and significantly improving oxygenation as well as static lung compliance. It seems that transpulmonary pressure is an effective way to reduce mortality and lung injury among patients with ARDS.

Additionally, we found that PEEP titrated by transpulmonary pressure was associated with tremendous improvement in lung compliance and oxygen exchange. This result was consistent with the research by Pirrone et al[42], which demonstrated the beneficial effect of transpulmonary pressure on improving respiratory function. These findings can be explained by the mechanism of transpulmonary pressure, which is the real parameter that accurately reflects the force acting on the pleural surface against lung tissue retraction under static conditions. Transpulmonary pressure plays a profound role in accurately reflecting the stress that alveoli suffered during MV accurately and is considered the force that prompted alveolar distension[43].

PEEP has been considered an indispensable therapy for ARDS patients. However, it is important to consider both the positive and negative aspects of this therapy. Higher PEEP inevitably has a negative correlation with hemodynamics when maintaining or restoring oxygenation[44]. In this study, the results showed that cardiac index became lower with the increase of PEEP, however, no differences were found between the two groups in blood pressure and heart rate. A clinical study conducted by Lai et al[45] demonstrated that reducing PEEP led to a significant increase in the cardiac index in both volume-responsive and volume-unresponsive patients. A suitable PEEP selected by monitoring transpulmonary pressure to decrease the effect on hemodynamics appears to be greatly important.

Meanwhile, we found that transpulmonary pressure was able to down-regulate the level of IL-6. As an essential means of life support, mechanical ventilation may not only bring benefits but also lead to the injury of lung tissue if improper use, which we call VILI. Although many factors account for VILI, the molecular mechanism under biotrauma has drawn public attention. In 2013, Ko et al[46] published a study showing that the incidence of VILI decreased with a decrease in IL-6 levels. This finding is consistent with our results. Therefore, considering all these results, we conclude that mechanical ventilation guided by transpulmonary pressure can reduce mortality by improving lung function and reducing inflammation.

Limitations

However, there were limitations in our meta-analysis. The small samples and the average low methodological quality of the study. Hence, more high-quality RCT studies are needed to certify the outcome and prognosis further.

Conclusions

Overall, this meta-analysis of 13 studies found that MV guided by transpulmonary pressure suggested beneficial effects on prognosis in patients suffering from ARDS. It not only improves oxygenation and ventilation parameters but also reduces the expression of inflammation mediators with minimal influence on hemodynamics.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Fang M.X. contributed to obtaining funding and study supervision. Zhang Q., Liu N and Li, Y. contributed to study selection, statistical analysis, data extraction, and quality assessment. Zhang Q. contributed to the charts-making and drafting of the article. Guo J.Y., Huang Q.S., Cao H., Wang Z.Y., Yin Z.Q., Liu M.Y., and Qi S.J. contributed to the revision of the article for important intellectual content. The article writing and figure elaboration were completed by all the authors together. All authors read and approved the final manuscript.

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Ethics Approval

This article does not contain any studies with human participants or animals. Therefore, ethics approval is not applicable.

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Data Availability

The data generated during the current study are available from PubMed, EMBASE, The Cochrane Library, The China National Knowledge Infrastructure, and WanFang database.

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